In examining claims during prosecution of a patent application, an Examiner must give each claim its broadest reasonable interpretation in light of the specification. However, this does not mean that limitations or examples in the specification can be read into the claims. In *Intervet America Inc. v. Kee-Vet Laboratories* 12 USPQ2d 1474 (Fed. Cir. 1989), the Federal Circuit has clearly indicated that it is improper to read limitations from the specification into the claims:

> ... this court has consistently adhered to the proposition that courts cannot alter what the patentee has chosen to claim as his invention, that limitations appearing in the specification will not be read into the claims, and that interpreting what is *meant* by a word in a claim "is not be confused with adding an extraneous limitation appearing in the specification, which is improper".

See also *Raytheon Co. v. Roper Corp.* 220 USPQ 592, 597 (Fed. Cir. 1983). ("That claims are interpreted in light of the specification does not mean that everything in the specification must be read into the claims.")

Contrary to the Examiner's position, the recitation in Claim 49 of "a method of regulating levels of osteoprotegerin" does not mean a "method of regulating levels of osteoprotegerin by gene therapy". To argue for this interpretation is to change the plain meaning of the claim, which is improper as a matter of law. The Examiner has not pointed to anything in the specification which would limit the claimed subject matter to a method of treatment using gene therapy. Applicants have specifically pointed to a use of the claimed method that does not involve treatment, namely increased production of an OPG polypeptide in a transgenic animal (see p. 12, line 26 of the specification). The Examiner has responded that "[p]roduction of osteoprotegerin in a transgenic animal does not appear to be the object of the claimed methods, since the claims do not recite production of a transgenic animal or recovery of the protein." It is not necessary that the claims be so limited in order to be enabled. Production of OPG by a transgenic mouse is simply one mode of carrying out the claimed invention, the invention being the regulation of OPG levels by modifying an animal with a gene encoding OPG. The Federal Circuit has held that "[t]he enablement requirement is met if the description enables any mode of making and using the invention" *Engel Indus., Inc. v. Lockformer Co.* 20 USPQ2d 1300, 1304 (Fed. Cir. 1991). Applicants have clearly enabled at least one mode of making and using the invention.

The Examiner's allegation of undue experimentation in view of the criteria set forth in *In re Wands* 8 USPQ2d 1401 (Fed. Cir. 1988) is unfounded. For instance, the Examiner contends that "[t]he state of the prior art as of 1995 was that gene therapy was not routinely successful" and has cited several references to suggest that gene therapy has not shown therapeutic benefit. Applicants disagree.

In the first instance, references published prior to 1995 showed numerous examples of successful gene therapy as reviewed by Yang et al. (Critical Rev. Biotech. 12, 335-356 (1992) attached hereto as Exhibit A). As stated in the abstract on p. 335:

> Genetically engineered retroviral vectors have been used successfully to infect live animals, effecting foreign gene expression in liver, blood vessels, and mammary tissues. Recombinant adenovirus and herpes simplex virus vectors have been utilized effectively for *in vivo* gene transfer into lung and brain tissues, respectively. [Applicants' emphasis]

The Yang reference cites numerous reports of gene transfer and regulation of foreign gene expression in various different tissues. In view of this, the Examiner's contention that gene therapy was "not routinely successful" in 1995 was not generally accepted by those skilled in the art

Secondly, enablement is not predicated on therapeutic benefit as a matter of law. The Patent and Trademark Office has clearly stated this position in Section 2164.05 of the MPEP:

> However considerations made by the FDA for approving clinical trials are different from those made by the PTO in determining whether a claim is enabled. See *Scott v. Finney* 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994).

However, the Patent Office will consider evidence submitted to FDA in support of initiating clinical trials in a determination of enablement. In this regard, it was well known in 1992 that human gene therapy clinical trials had been started (see Miller Nature 357, 455-460 (1992) attached hereto as Exhibit B) and this fact provides additional evidence that gene therapy was enabled as of the priority date.

Finally, the Patent and Trademark Office has previously issued broad claims to gene therapy methods. For example, U.S. Patent No. 5,399,346 (hereafter the '346 patent, attached hereto as Exhibit C) issued to Anderson et al. on March 21, 1995 claims *ex vivo* gene therapy of a human therapeutic protein in a human cell. Based on the issuance of the '346 patent, it was clear that the United States Patent and Trademark Office prior to 1995 believed that *ex vivo* gene therapy were so broadly enabled as to encompass any human cell and any human therapeutic protein. This is further evidence that gene therapy was indeed considered to be routinely successful in 1995.

Similar arguments have been raised by the Examiner against anti-sense therapy, namely that anti-sense regulation of OPG expression is allegedly not enabled because there were no anti-sense drugs on the market in 1995. As with gene therapy, FDA approval of an anti-sense therapy for a disease is not a determinant of enablement. Moreover, the Examiner's own references actually show numerous examples of successful anti-sense regulation of gene expression. Applicants have provided the nucleic

acid sequences encoding rat and human OPG and methods for expression of said nucleic acid sequences. This disclosure combined with anti-sense techniques available in the art combined with the level of skill in the art would enable one to regulate OPG levels in an animal by anti-sense without undue experimentation.

The Examiner argues that the claims are "broad" and that the art is unpredictable "because there is no evidence of similar proteins being expressed to effect a therapeutic treatment". It is unclear what criteria the Examiner is using to allege that the claims are "broad". The present claims relate to a method of regulating OPG, not any therapeutic protein and, in one respect, are not as broad as the claims issued in the '346 patent. Moreover, the Yang reference provides evidence for regulating levels of other proteins by gene transfer. In addition, evidence of therapeutic treatment by gene transfer is not a factor in determining enablement since the claims are not limited to OPG levels that show therapeutic benefit.

In review the *Wands* criteria, the Examiner states that the most important factor is the lack of guidance in the specification "regarding how to practice a gene therapy method". In *Wands*, guidance and direction in the application applies to the practice of the invention. The present invention is related to regulation of OPG levels and is not limited to gene therapy. Consequently, an example of any method of regulating OPG levels by modifying an animal with a gene encoding OPG provides guidance and direction in practicing the invention. Applicants have provided such an example and have clearly demonstrated one method of carrying out the claimed invention.

The Examiner asks "what teachings in the specification" enable the claimed methods. Applicants maintain that the disclosure of nucleic acid sequences encoding OPG, expression of OPG, and transgenic mice expressing OPG, combined with the level of skill in the art, enable the full scope of the claimed invention.

Applicants maintain that the Examiner's reasoning lacks support in fact and in law and that a *prima facie* case of nonenablement has not been established. In view of the above remarks, Applicants respectfully request that the rejection be withdrawn.

Declaration of Jackie Z. Sheng

If it should be determined that a *prima facie* case of nonenablement has been established by the Examiner, Applicants submit herewith as Exhibit D a Declaration by Dr. Jackie Z. Sheng which shows that introduction of an adenovirus vector expressing a human OPG fusion protein protects against bone loss in ovariectomized rats. It is believed that the results presented in the Declaration are sufficient to rebut any *prima facie* case of nonenablement.

CONCLUSION

It is believed that Claims 49-53 are in condition for allowance and an early notice thereof is solicited.

Respectfully submitted,

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